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Supporting Information

ACE2-Variants Indicate Potential SARS-CoV-2-Susceptibility in Animals: A Molecular Dynamics Study

Szymon Pach⁺, Trung Ngoc Nguyen⁺, Jakob Trimpert, Dusan Kunec, Nikolaus Osterrieder,* and Gerhard Wolber*© 2021 The Authors. Molecular Informatics published by Wiley-VCH GmbH. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

Supporting Information

ACE2-Variants Indicate Potential SARS-CoV-2-Susceptibility in Animals: An Extensive Molecular Dynamics Study

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Table S1: Principle component (PC) analysis of eight selected molecular descriptors.

Feature	Eigenvalue	Variance [%]	
PC 1	1.93	24.1	
PC 2	1.67	20.8	
PC 3	1.27	15.9	
PC 4	1.07	13.3	
PC 5	0.74	9.2	
PC 6	0.62	7.8	
PC 7	0.40	5.0	
PC 8	0.32	3.9	

		В	рС			Вр В		Вр А
Feature	Depth	Defor- mation	χ1 Angle ACE2- F/Y82/83	Lipophilic contacts S-F486 – ACE2- F/Y82/83	Distance S-Q493 – ACE2- residue 30/31	Distance ACE2- residues 30/31 – 34/35	Distance S-K417 – ACE2- residue 29/30	Hydrogen bond count
PC 1	12,9%	2,4%	6,5%	5,5%	26,9%	31,0%	6,5%	8,2%
PC 2	18,8%	0,1%	24,5%	23,2%	2,7%	0,5%	13,6%	16,6%
PC 3	0,1%	30,6%	24,0%	1,3%	16,5%	7,8%	8,7%	10,9%
PC 4	21,2%	44,5%	0,0%	0,2%	2,3%	7,2%	20,1%	4,4%
PC 5	13,1%	0.5%	1,2%	64,1%	4,1%	4,3%	6,7%	6,0%
PC 6	0,4%	1,8%	0,0%	0,1%	0,0%	0,8%	43,1%	53,8%
PC 7	6,6%	12,9%	18,0%	0,5%	26,8%	34,2%	0,8%	0,2%
PC 8	26,9%	7,1%	25,7%	5,2%	20,6%	14,1%	0,5%	0,0%

Abbreviations: ACE2- Angiotensin-converting enzyme 2, Bp- binding pocket, PC- principle component, S- spike. Red numbers represent the highest value in a row, the orange numbers the second-highest value.

	255 26 30 38 40 48 80 88 80 88 30 78 60 68 60 68 400 408 615 418
Human	STIEEQÄKTFLÜKFNHEAEDLFYQSSLASHNYNTNITEENVÕNMNNAGDKNŠAFLKEQSTLAQMYPLQEIQNLTVKLQLQALQQNGSSVLSEDKSKRLNT 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 105 110 115
Dog	QSŤEDLVŘTFLEŘFNYEÁEELSÝQSSLÁSWNYŇINITĎENVQŘMNNAĞAKWSÁFYEEQSKLAŘTYPLĚEIQDŠTVKRQLRALQHSGSŠVLSAĎKNQRĽNT
Cat	20 25 30 35 40 45 50 55 60 57 75 80 85 90 95 100 105 110 115 STEELAKTFLEKFNHEAEELSYQSSLASNNYNTNITDENVQKMNEAGAKWSAFYEEQSKLAKTYPLAEINNTTVKRQLQALQQSGSSVLSADKSQRLNT 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 105 110 115
Ferret	20 25 30 35 40 45 50 55 60 57 75 80 85 90 96 100 105 110 115 STEDLAKTFLEKFNYEAELSYQNSLASNNYNTNITDENIQKMNIÄGAKWSAFYEESQHÄKTYPLEEIQPPIIKRQLRALQQSGSSVLSADKRERLNT 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 105 110 115
Syrian hamster	20 25 30 35 40 45 50 55 60 55 70 75 80 85 90 95 100 105 110 115 SIIEEQÄKTFLÖKFNQËAEDLSYQSALASHNYNTNITEENAQKMNEÄAAKWSAFYEËQSKLÄKNYSLQEVQNLTIKRQLQALQQSGŠSALSADKNKQLNT 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 105 110 115
Mouse	20 25 30 35 40 45 50 55 60 57 77 75 80 85 90 95 100 105 110 115 SITEENAKTFLNNFNQEAEDLSYQSSIASHNYNTNITEENAQKMSEAAAKWSAFYEEQSKTÄQSFSLQEIQTPIIKRQLQALQQSGSSALSÄDKNKQLNT 20 25 30 35 40 45 50 55 60 55 70 75 80 85 90 95 100 105 110 115 110 115
Rat	20 25 30 35 40 45 50 55 60 55 70 75 80 85 90 95 100 105 110 115 SLIEEKÄESFLNKFNQËAEDLSYQSSLASNYNTNITEENAQKMNEÄAAKWSAFYEËQSKIÄQNFSLQEIQNATIKRQLKALQQSGSSALSPDKNKQLNT 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 105 110 115
Rea squirrei	20 25 30 35 40 45 50 55 60 55 70 75 80 85 90 95 100 105 110 115 STIEESÄKTFLÜKFNQEAEDLSYQSSLASHDYNTNISEKNAQKMNEÄGAKWSAFYEEQSKLÄKTYPLQQIQNLTVKRQLQALQQSGSSVLSTDKQKQLNT 20 25 30 35 40 45 50 65 60 65 70 75 80 85 90 95 100 105 110 115
	20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 105 110 115 SIIEEQÄKTFLDKFNQEAEDLSYQSALASHNYNTNITEENAQKMNEAAAKWSAFYEEQSKLÄKNYSLQEVQNLIIKRQLQALQQSGSSALSÄDKNKQLNT 10 15 20 25 30 35 40 45 50 85 60 65 70 75 80 85 90 95 100 125
	STIEEQAKTFLDKFNQEÄEDLSŸQSSLÄSHNYNTNITEENAQKMNEAÄAKHSÄFYEEQSKLAKNYPLÓDVQNLTIKRÖLQALÖQSGSŠALSADKNKQÜNT 1750 1758 1750 1758 1750 1750 1750 1750 1750 1750 1750 1750
numan	TÜNTMSTIYSTĞKYĞNPDNPQEĞLLLEPGLNETMANSLDYNERLHANESHNSEVGKÜLRPLYEEYVÜLKNEMARAN - HYEDYĞDYHRĞDYEVNGVDĞYD 120 125 126 126 126 120 120 120 120 120 120 120 120 120 120
Cat	ILINSTYVYSTGKAČNPSPPQECILLEPGLDDIMENSKOYNERLINANEGWRSEVGKQLRPLYEEVYALKNEMARANMYEDYGDYWRGDYEEEWENGYN 120 125 130 135 140 145 150 155 160 165 170 175 180 185 190 185 200 205 210 215 ILINAMSTIYSTGKAČNPNNPQECILLEPGLDDIMENSKOYNERLINANEGWRAEVGKQLRPLYEEYYALKNEMAKSKQVNYEDYGDYWRGDYEEEWTDGYN
Forret	ILNAMSTIYSTGKAGNPNNPQECLLLEPGLDDIMENSKDYNERLWAWEGWRAEVGKQLRPLYEEYVALKNEMAKSKQVNYEDYGDYWRGDYEEEWTDGYN 120 125 130 135 140 145 150 155 160 155 170 175 180 185 190 156 200 205 210 215
Syrian hamster	120 128 130 135 140 145 150 158 160 165 170 175 180 180 180 190 185 200 205 210 215 ILNAMSTIYSTGKAĞNPNNPQEĞLLLEPGLDDIMENSKOPWERLWANEGWRSEVGKQLRPLYEEYVALKNEMARAN-NYEDYGDYNGGYEEWADGYS 120 125 130 135 140 145 150 155 160 165 170 175 180 185 190 195 200 205 210 215 ILNTMSTIYSTGKVĞNPKNPQEĞLLLEPGLDIMATSTDYNERLWAWEGWRAEVGKQLRPLYEEYVVLKNEMARAN-NYEDYGDYNRGDYEAEGADGYN
Mouse	120 125 130 135 140 141 150 155 160 165 170 175 180 185 190 195 200 205 210 215 ILNTMSTIYSTGKV <mark>C</mark> NPKNPQECLLLEPGLDEIMATSTDYNSRLWAWEGWRAEVGKQLRPLYEEYVVLKNEMARANNYNDYGDYNRGDYEAEGADGYN
Rat	120 125 130 135 140 145 150 155 160 165 170 175 180 185 190 195 200 205 210 215 ILNTMSTIYSTGKVCNSMNPQECFLLEPGLDEIMATSTDYNRRLWAWEGWRAEVGKQLRPLYEEYVVLKNEMARANNYEDYGDYNRGDYEAEGVEGYN
Red squirrel	120 125 130 135 140 145 150 175 175 180 185 190 185 190 185 190 185 190 185 190 205 210 215 LLMMSTIYSTGKVÜNPNKPQEELLLEPGLDDIMANSTDYNERLWWEGWRSEVGKQLRPLYEEVVUKKEMARANDYEDYGDYWRGDYEAEGADGYG 120 125 130 135 140 145 150 155 150 165 170 175 180 186 190 185 200 205 210 215
Chinese hamster	120 125 130 135 140 145 150 155 160 165 170 175 180 185 180 185 200 205 210 215 Lintwstystgkupkmpcellllepglddimatstdymerrwaserskolerplyeevvikmemaran-mykdyddymergyeaecadayn 110 115 120 125 130 135 140 145 150 155 160 165 170 165 170 185 190 185 200 205
Campbell's dwarf hamster	110 115 120 125 130 135 140 145 150 155 160 165 170 175 180 185 190 195 200 205 ILNTMSTÏYSTGKY <mark>C</mark> NPKNPQEC <mark>C</mark> LLLEPGLDDİMATSTDYNERLWAWEGWRAEVGKQLRPLYEEYVVLKNEMARANNYKDYGDYWRGDYEAEGENGYN
Human	220 225 230 235 240 245 250 255 260 255 260 265 270 275 260 285 290 285 290 295 300 305 310 315 YSRGQLIEDVEHTFEEIKPLYEHLHAYVRAKLMNAYPSYISPIGCLPAHLLGDMNGRFWTNLYSLTVPFGQKPNIDVTDAMVDQAWDAQRIFKEAEKFFV
Dog	270 225 230 235 240 245 250 255 250 255 250 255 270 275 280 285 290 255 300 355 310 315 YSRNQLIDDVELTFTQIMPLYQHLHAYVRTKLMDTYPSYISPTGCLPAHLLGDMNGRFNTNLYPLTVPFGQKPNIDVTNAMVNQSWDARKIFKEÄEKFFV
Cat	220 225 230 235 240 245 250 255 260 265 270 275 280 285 290 285 300 355 310 315 YSRSQLIKDVEHTFTQIKPLYQHLHAYVRAKIMDTYPSRISPTGCLPAHLLGDMNGRFNTNLYPLTVPFGQKPNIDVTDAMVNQSNDARRIFKEAEKFFV
	220 225 230 238 240 245 250 255 260 265 270 275 280 285 290 285 300 305 310 315 YSRNQLIEDVEHTFTQIKPLYEHLHAYVRAKLMDAYPSRISPTGCLPAHLLGDMNGRFHTNLYPLMVPFRQKPNIDVTDAMVNQSWDARRIFEEAETFFV
	20 20 20 20 20 20 20 20 20 20 20 20 20 2
	YNRKQLIEDVERTFREIKFLYEHLHAYVRRKLMDTYPSYISPTGCLPAHLLGDMNGRFHTNLYPLTYPFAQKPMIDVTDAMMNGGMDAERIFQEAEKFFV
Rat	220 225 230 235 240 245 250 255 260 265 270 275 280 285 290 295 300 305 310 315 YNRNQLIEDVENTFKEIKPLYEQLHAYVRTKLMEVYPSYISPTGCLPAHLLGDMWGRFWTNLYPLTTPFLQKPNIDVTDAMVNQSWDAERIFKEAEKFFV
Red squirrel	230 235 230 235 240 245 250 255 260 265 270 275 280 285 290 295 300 305 310 315 VNRNQLIEDVERTFAEIKPLYEHLHAYVRAKLMDTYPSYISPTGCLPAHLLGDMNGRFNTNLYSLTVPFQEKPNIDVTDAMMNQNNDAMRIFKEAEKFFV
Chinese hamster	230 235 230 235 240 245 250 255 260 265 270 275 280 285 290 295 300 305 310 315 YNGNQLIEDVERTFKEIKPLYEQLHAYVRTKLMDTYPSYISPTGCLPAHLLGDMWGRFWTNLYPLTVPFGQKPNIDVTDAMVNQGWDAERIFKEAEKFFV
Campbell's dwarf hamster	210 215 220 225 230 235 240 245 250 255 250 255 250 255 270 275 280 285 290 255 300 305 VNGNQLIEDVERTFKEIKPLYEQLHAYVRTKLVNTYPSYISPTGCLPAHLLGDMWGRFNTNLYPLTVPFGQKPNIDVTDAMVKQGWGAERIFKEAEKFFV
Human	SVGLPNMTQGFHENSMLTDPGNVQKAV <mark>C</mark> HPTAHDLGKGDFRILM <mark>C</mark> TKVTMDDFLTAHHEMGHIQYDMAYAAQPFLLRNGANEGFHEAVGEIMSLSAATPK
Dog	320 325 330 335 340 345 350 355 360 365 370 375 380 385 390 395 400 405 410 415
Dog	SVGLPNMTQÉFMGNŠMLTEPSOSRŘVV <mark>C</mark> HPTANDÍGKGDFRIKM <mark>Č</mark> TKVTMDDELŤAHHEMGHIQÝDMAYÁAQPFĹLRNGÁNBEGFHEAVGEIMSLŠAATPŇ
Cat	320 325 330 335 340 345 350 355 360 365 370 375 380 385 390 365 400 405 410 415 SVGLPMTQGFWENSHLTEPGDSRKVV <mark>G</mark> HPTAWDLGKGDFRIKW <mark>G</mark> TKVTMDDFLTAHHERGHIQYDMAYAVQPFLLRNGANEGFHEAVGEIMSLSAATPM
Cat	320 325 330 335 340 345 350 355 360 365 370 375 380 385 390 365 400 405 410 415 SVGLPMTQGFWENSHLTEPGDSRKVV <mark>G</mark> HPTAWDLGKGDFRIKW <mark>G</mark> TKVTMDDFLTAHHERGHIQYDMAYAVQPFLLRNGANEGFHEAVGEIMSLSAATPM
Cat Ferret Syrian hamster	320 325 330 335 340 345 330 356 390 395 370 375 380 395 390 395 400 495 410 415
Cat Ferret Syrian hamster Mouse	320 325 330 335 340 345 350 356 350 355 350 356 350
Cat Ferret Syrian hamster Mouse Rat	320 325 330 335 340 345 350 356 350
Cat Ferret Syrian hamster Mouse Rat Red squirrel	320 325 330 335 340 345 350 355 355
Cat Ferret Syrian hamster Mouse Rat Red squirrel Chinese hamster	320 325 330 335 340 345 350 355 390 355 330 335 330 335 330 335 340 345
Cat Ferret Syrian hamster Mouse Rat Red squirrel Chinese hamster Campbell's dwarf hamster	320 325 330 335 340 345 350
Cat Ferret Syrian hamster Mouse Rat Red squirrel Chinese hamster Campbell's dwarf hamster Human	320 325 330 335 340 345 350 356 356 356 356 356 356 356 356 356 356 356 356
Cat Ferret Syrian hamster Mouse Rat Red squirrel Chinese hamster Campbell's dwarf hamster Human Dog	329 329 330 345 340 345 350
Cat Ferret Syrian hamster Mouse Rat Red squirrel Chinese hamster Campbell's dwarf hamster Human Dog Cat	320 325 330 335 340 345 350 356 356 356 350 356
Cat Ferret Syrian hamster Mouse Rat Red squirrel Chinese hamster Campbell's dwarf hamster Human Dog Cat Ferret	320 325 330 345 340 345 350
Cat Ferret Syrian hamster Mouse Rat Red squirrel Chinese hamster Campbell's dwarf hamster Human Dog Cat Ferret Syrian hamster	230 235 330 335 340 345 350 356 350
Cat Ferret Syrian hamster Mouse Rat Red squirrel Chinese hamster Campbell's dwarf hamster Human Dog Cat Ferret Syrian hamster	230 235 330 335 340 345 350 356 350
Cat Ferret Syrian hamster Mouse Rat Red squirrel Chinese hamster Campbell's dwarf hamster Human Dog Cat Ferret Syrian hamster Mouse Rat	290 295 390 395 340 345 350
Cat Ferret Syrian hamster Mouse Rat Red squirrel Chinese hamster Campbell's dwarf hamster Human Dog Cat Ferret Syrian hamster Mouse Rat Red squirrel	202 325 330 335 340 345 350 355 350
Cat Ferret Syrian hamster Mouse Rat Red squirrel Chinese hamster Campbell's dwarf hamster Human Dog Cat Ferret Syrian hamster Mouse Rat Red squirrel Chinese hamster	202 325 330 335 340 345 350 355 350
Cat Ferret Syrian hamster Mouse Rat Red squirrel Chinese hamster Campbell's dwarf hamster Human Dog Cat Ferret Syrian hamster Mouse Rat Red squirrel Chinese hamster Campbell's dwarf hamster	290 295 390 395 396 396 396 396 396 396 396 396 396 490 496 410 415
Cat Ferret Syrian hamster Mouse Rat Red squirrel Chinese hamster Campbell's dwarf hamster Human Dog Cat Ferret Syrian hamster Mouse Rat Red squirrel Chinese hamster Human Cog Cat Ferret Syrian hamster Mouse Rat Red squirrel Chinese hamster Campbell's dwarf hamster Human	320 325 330 335 340 345 350 356 350
Cat Ferret Syrian hamster Mouse Rat Red squirrel Chinese hamster Campbell's dwarf hamster Human Dog Cat Ferret Syrian hamster Mouse Rat Red squirrel Chinese hamster Campbell's dwarf hamster Human Dog	320 325 330 335 340 345 350 356 350
Cat Ferret Syrian hamster Mouse Rat Red squirrel Chinese hamster Campbell's dwarf hamster Human Dog Cat Ferret Syrian hamster Mouse Rat Red squirrel Chinese hamster Campbell's dwarf hamster Human Dog Cat Ferret Syrian hamster House Rat Red squirrel Chinese hamster Campbell's dwarf hamster Human Dog Cat	290 295 390 395 340 345 350 395 390 395 390 395 390 395 390 395 400 495 410 415
Cat Ferret Syrian hamster Mouse Rat Red squirrel Chinese hamster Campbell's dwarf hamster Human Dog Cat Ferret Syrian hamster Mouse Rat Red squirrel Chinese hamster Campbell's dwarf hamster Human Dog Cat Ferret Syrian hamster Mouse Rat Red squirrel Chinese hamster Campbell's dwarf hamster Human Dog Cat Ferret	329 329 339 349 345 350 355 360 355 360 355 330 345 330 345 340 445
Cat Ferret Syrian hamster Mouse Rat Red squirrel Chinese hamster Campbell's dwarf hamster Human Dog Cat Ferret Syrian hamster Mouse Rat Red squirrel Chinese hamster Mouse Rat Chinese hamster Campbell's dwarf hamster Human Dog Cat Ferret Syrian hamster	320 320 330 340 346 350 356 350 356 370 375 380 385 390 495 490 495 320 320 330 335 340 346 340 345 330 336 330 336 400 445 320 325 330 335 340 346 340 345 330 336 330 336 430 440 320 320 330 335 340 346 340 345 330 336 330 336 430 440 320 320 330 335 340 346 340 346 340 345 320 320 330 335 340 346 340 346 340 345 320 320 330 335 340 346 340 346 340 345 320 320 330 335 340 346 340 346 340 345 320 320 330 335 340 346 340 346 340 346 320 320 330 335 340 346 340 346 340 346 320 320 330 330 330 330 340 346 340 346 320 320 330 330 330 330 340 346 340 346 320 320 330 330 330 330 340 346 340 346 320 320 330 330 330 330 330 330 330 330 330 330 330 330 320 320 320 330 330 330 330 330 330 330 330 330 330 320 320 320 320 330 330 330 330 330 330 330 330 330 330 330 320 320 320 320 33
Cat Ferret Syrian hamster Mouse Rat Red squirrel Chinese hamster Campbell's dwarf hamster Human Dog Cat Ferret Syrian hamster Mouse Rat Red squirrel Chinese hamster Campbell's dwarf hamster Human Dog Cat Ferret Syrian hamster Chinese hamster Campbell's dwarf hamster Human Dog Cat Ferret Syrian hamster Mouse	320
Cat Ferret Syrian hamster Mouse Rat Red squirrel Chinese hamster Campbell's dwarf hamster Human Dog Cat Ferret Syrian hamster Mouse Rat Red squirrel Chinese hamster Mouse Campbell's dwarf hamster Campbell's dwarf hamster Campbell's dwarf hamster Ferret Syrian hamster Human Dog Cat Ferret Syrian hamster Mouse Rat Red squirrel Chinese hamster Campbell's dwarf hamster Human Dog Cat Ferret Syrian hamster Mouse Rat	320
Cat Ferret Syrian hamster Mouse Rat Red squirrel Chinese hamster Campbell's dwarf hamster Human Dog Cat Ferret Syrian hamster Mouse Rat Red squirrel Chinese hamster Mouse Campbell's dwarf hamster Ferret Syrian hamster Chinese hamster Chinese hamster Campbell's dwarf hamster Human Dog Cat Ferret Syrian hamster Mouse Rat Red squirrel Red squirrel	120
Cat Ferret Syrian hamster Mouse Rat Red squirrel Chinese hamster Campbell's dwarf hamster Human Dog Cat Ferret Syrian hamster Mouse Rat Red squirrel Chinese hamster Campbell's dwarf hamster Human Dog Cat Ferret Syrian hamster Chinese hamster Ferret Syrian hamster Human Dog Cat Ferret Syrian hamster Human Red squirrel Cat Ferret Syrian hamster Mouse Rat Red squirrel Chinese hamster	320

Figure S1: Sequence alignment of human and animal angiotensin-converting enzyme 2 performed with MOE 2019.0102 (Molecular Operating Environment, Chemical Computing Group ULC, Montreal, Canada). Colour code: yellow box- cysteine residues involved in a disulfide bridge.

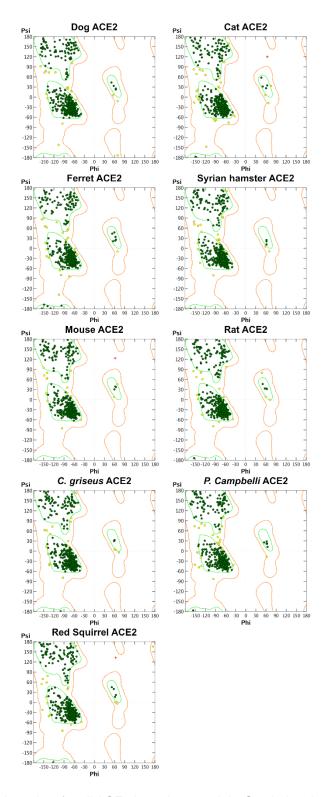


Figure S2: Ramachandran plots for all ACE2 homology models. Symbol code: green point- residue with favourable geometry, yellow point- residue with allowed geometry, red cross- outlier. The figure was generated using MOE 2019.0102 (Molecular Operating Environment, Chemical Computing Group ULC, Montreal, Canada).

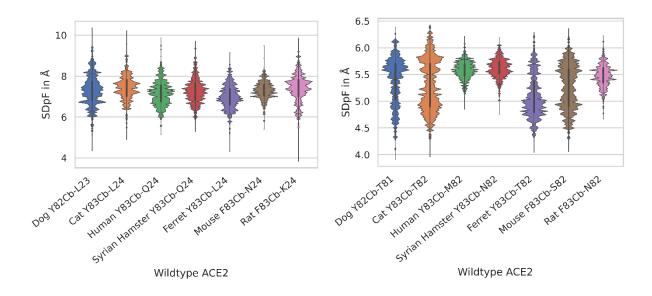


Figure S3: Distance distribution between Bp C key residues for analyzed wildtype ACE2 species. Shortest Distance per Frame (SDpF) between the Cb atom of residue 83 (or 82 in dog) and side chains flanking the binding pocket C (residues 24 and 82 or 23 and 81 in dog) representing the 'depth' of Bp C.

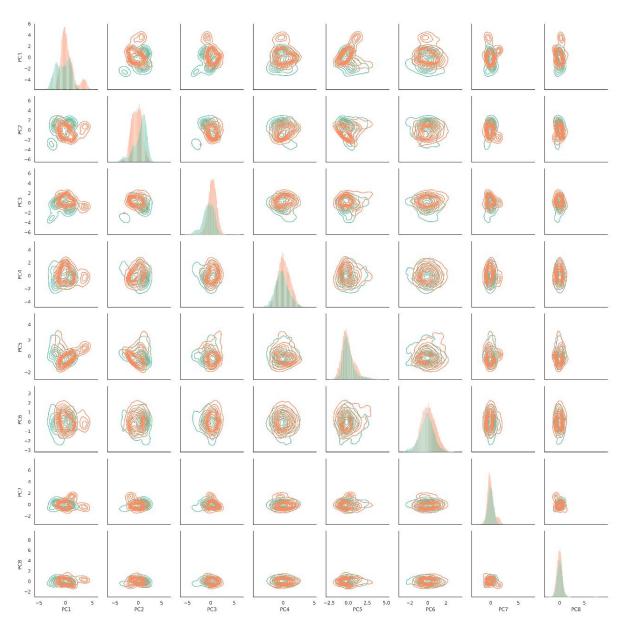


Figure S4: Histograms of principle components (PC) and kernel density plots of PC pairs visualizing the variance dependent ability of our feature set to discriminative between susceptible (orange lines) and non-susceptible species (green lines).

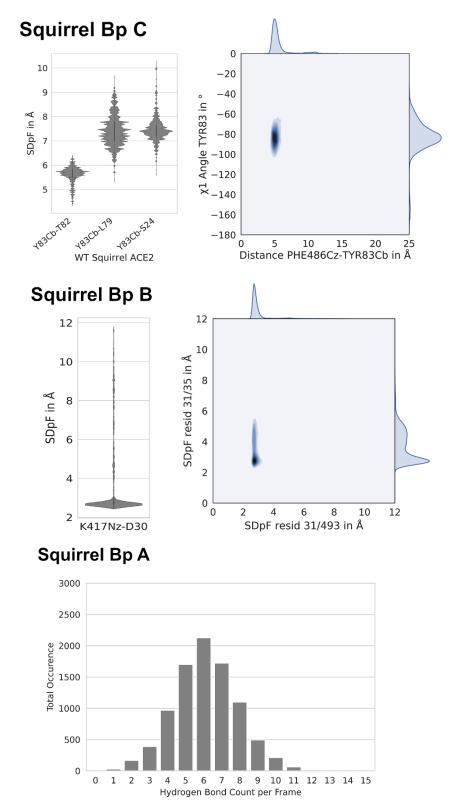
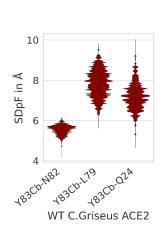
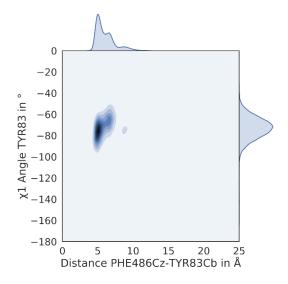


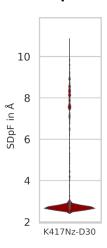
Figure S5. Descriptors calculated for red squirrel ACE2-RBD simulations. **Bp C**: Shortest Distance per Frame (SDpF) between Cb atom of Y83 and side chains of residues flanking the binding pocket; **Bp B**: Distance distribution for interactions between Nz atom of RBD K417 and the side chain of ACE2 residue 30, and kernel density plots summarizing the interactions between ACE2-residue 31 and RBD residue Q493; **Bp A**: histograms representing the total occurrence of hydrogen bonds in binding pocket A between ACE2 residues 37, 38, 41, 42, 353, 355 and RBD residues 449, 496, 498, 500, 501, 505.

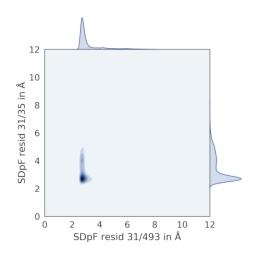
C. griseus Bp C



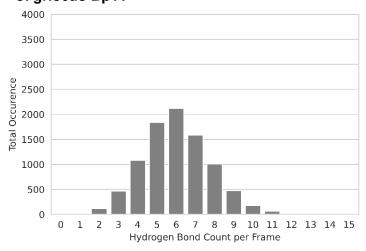


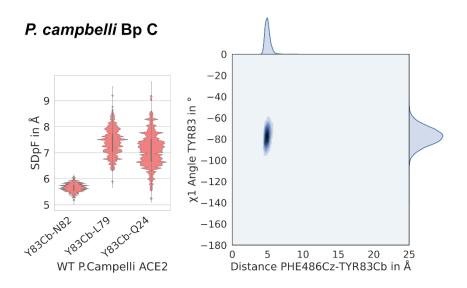
C. griseus Bp B



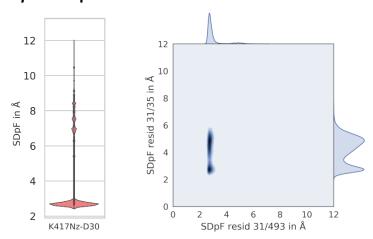


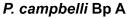
C. griseus Bp A





P. campbelli Bp B





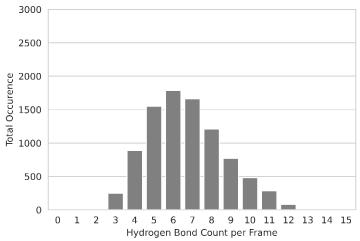


Figure S6. Descriptors calculated for small hamsters (*C. griseus*, *P. campbelli*) ACE2-RBD simulations. **Bp C**: Shortest Distance per Frame (SDpF) between Cb atom of Y83 and side chains of residues flanking the binding pocket; **Bp B**: Distance distribution for interactions between Nz atom of RBD K417 and the side chain of ACE2 residue 30, and kernel density plots summarizing the interactions between ACE2-residue 31 and RBD residue Q493; **Bp A**: histograms representing the total occurrence of hydrogen bonds in binding pocket A between ACE2 residues 37, 38, 41, 42, 353, 355 and RBD residues 449, 496, 498, 500, 501, 505.

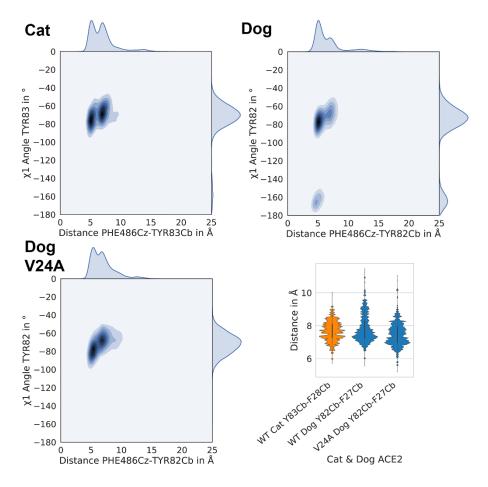


Figure S7. Occupation of binding pocket C indicated by kernel density plots (x-axis: distance F486 Cz - Y82 Cb; y-axis: χ1 angle of central residue 82/83) and Bp C deformation of in dog ACE2 wild type, V24A mutant, and homologous residue 83 in cat (Y83/82 Cb – F28/27 Cb distance).

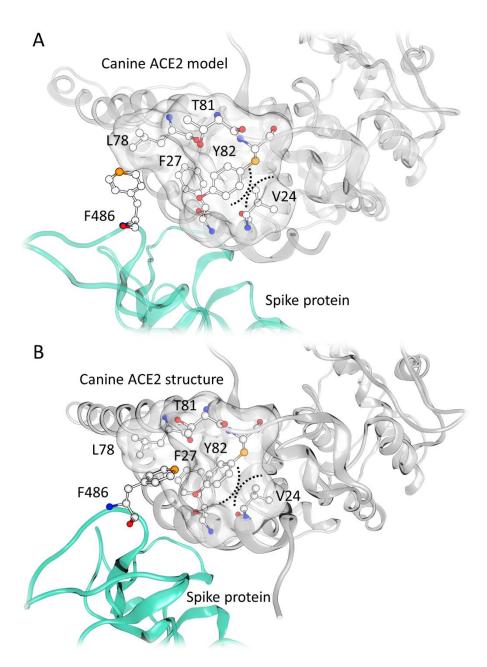


Figure S8. Comparison of (A) the "fixed state" in our model of canine angiotensin-converting enzyme 2 (ACE2) in complex with viral spike protein extracted from a molecular dynamics simulation and (B) the cryoscopic electron microscopy structure of the dog ACE2 in complex with the viral spike protein.

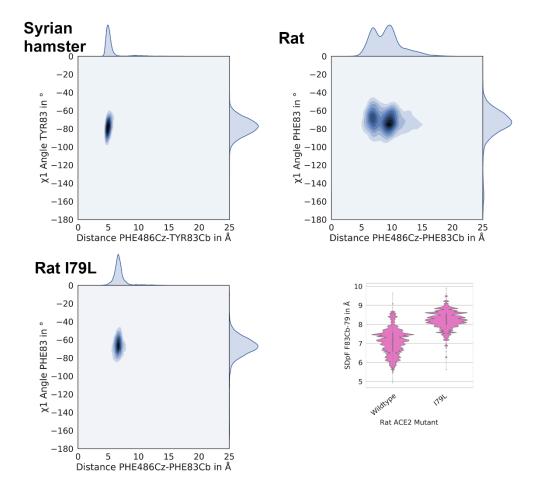
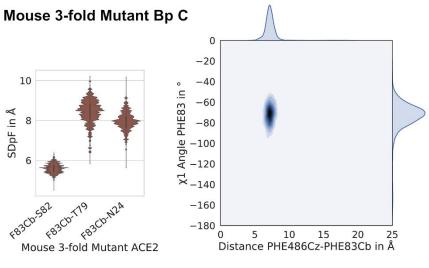
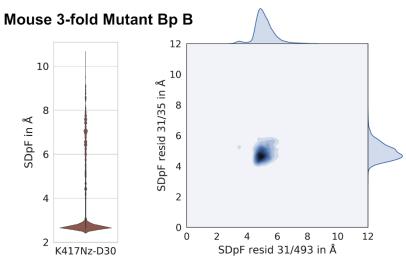
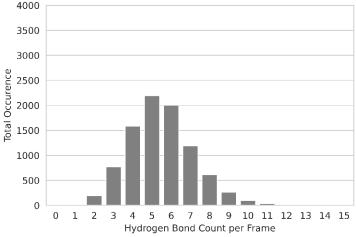


Figure S9. Kernel density plots summarizing the occupation of binding pocket C (x-axis, surrogate parameter: distance F486 Cz - Y83 Cb) and rotamers of central residue 82 (or 83 in cats). The lower right panel shows the opening of the Bp C based on the SDpF-83-79 (Shortest Distance per Frame) parameter.









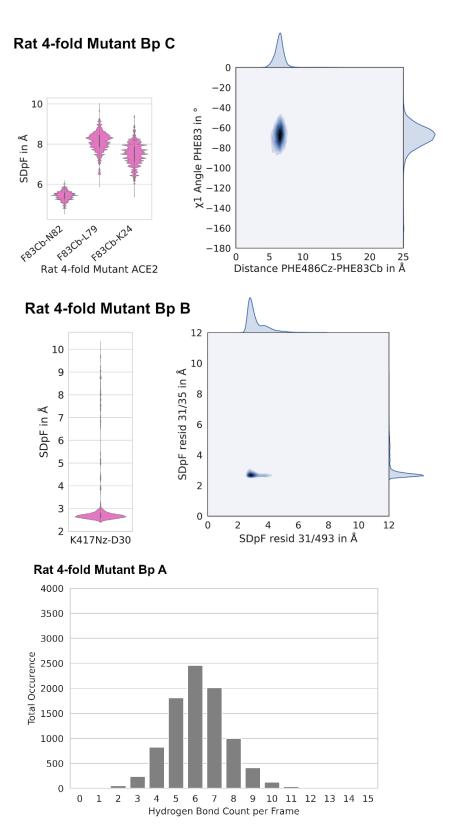


Figure S10. Descriptors calculated for mouse triple mutant (upper panels) and rat quadruple mutant (lower panels) ACE2-RBD simulations. **Bp C**: Shortest Distance per Frame (SDpF) between Cb atom of Y83 and side chains of residues flanking the binding pocket; **Bp B**: Distance distribution for interactions between Nz atom of RBD K417 and the side chain of ACE2 residue 30, and kernel density plots summarizing the interactions between ACE2-residue 31 and RBD residue Q493; **Bp A**: histograms representing the total occurrence of hydrogen bonds in binding pocket A between ACE2 residues 37, 38, 41, 42, 353, 355 and RBD residues 449, 496, 498, 500, 501, 505.